Kendle

September 13, 2007

Division of Dockets Management
Food and Drug Administration (HFA-305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition on behalf of Sun Pharmaceuticals Limited in quadruplicate, pursuant to 21 CFR 10.30 and in accordance with the regulations at 21 CFR 314.161, requesting the Commissioner of the Food and Drug Administration to provide a determination whether the listed drug product ZOMETA (Zoledronic acid for injection) containing Zolendronic acid 4 mg per vial has been withdrawn for safety or effectiveness reasons as outlined in the attached.

Respectfully submitted,

Anthony C. Celeste

Anthony C. Celeste
Senior Vice President
Kendle International
On behalf of
Sun Pharmaceuticals, Ltd.

Enclosure

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2007P-0341 CP1

Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 6615500, 6615600, 6615700
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SUN
PHARMACEUTICAL
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SUITABILITY PETITION

The undersigned, submits this petition under section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.93 and 21 CFR §10.30 to request the Commissioner of Food and Drugs to make a determination that the formulation of ZOMETA® (Zoledronic acid for injection) containing sterile lyophilized powder in a vial, is suitable for submission as an Abbreviated New Drug Application (ANDA).

A. Action Requested

The petitioner requests the Commissioner of Food and Drugs to make a determination that the formulation of ZOMETA ® (Zoledronic acid for injection) containing Zoledronic acid 4 mg per vial were not withheld from sales for safety and efficacy reasons. The petitioner particularly requests the FDA to make a determination that the proposed generic product referring to the originally approved formulation (now not available in market. Letter from dealer indicating this has been provided as Exhibit-1) would not render the product less safe or effective than the currently marketed innovator's product (liquid concentrate injection). The petitioner further requests the FDA to accept Abbreviated New Drug Application (ANDA) for Zoledronic acid powder for Infusion (hereinafter referred to as "proposed generic product") containing Zoledronic acid 4 mg /vial for the reasons discussed herein below.

B. Statement of Grounds

I. Background:

The active ingredient in ZOMETA ® (Zoledronic acid injection) is Zoledronic acid, an inhibitor of osteoclastic bone resorption. Zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. It also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. It inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. Lyophilized form and liquid concentrate form of Zometa are listed in orange book as RLD, under NDA 21-223. The copy of internet Orange book indicating RLD status for both lyophilized form and liquid concentrate form is provided herewith as Exhibit-2. The qualitative and quantitative composition of lyophilized RLD (4 mg base/vial), after reconstitution is identical to that of liquid concentrate form of RLD (4 mg base/5 ml)

The proposed generic product have been developed as lyophilized form. Due to unavailability of lyophilized form of RLD in the market, the liquid concentrate form has been considered as reference for the proposed labeling and pharmaceutical equivalence studies, conducted for requesting the biowaiver pursuant to 21 CFR 320.22(b)(1).

Originally approved formulation :

Zometa® (Zoledronic acid for injection) containing Zoledronic acid, manufactured by Novartis Pharma was first approved on August 20, 2001 under NDA 021-223. It was recommended that each vial of Zometa be reconstituted by adding 5 mL of Sterile Water for Injection, USP, to each vial. The resulting solution allows for withdrawal of 4 mg of zoledronic acid. The drug must be completely dissolved before the solution is withdrawn. The maximum recommended 4 mg-dose must be further diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. The dose must be given as a single intravenous infusion over no less than 15 minutes. The copy of approved labeling ,dated 22 February, 02, for lyophilized Zometa® (Zoledronic acid for injection), is provided herewith as Exhibit-3.

Corporate Office : ACME PLAZA, Andheri Kurla Road, Andheri(E), Mumbai - 400 059 INDIA.
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Second formulation: Supplemental application, provided for liquid dosage form of the previously approved lyophilized powder for injection, was approved on 07, March 2003 . The concentrate for injection is to be further diluted with 100 mL of sterile 0.9 % Sodium Chloride, USP, or 5% Dextrose Injection, USP. The dose must be given as a single intravenous infusion over no less than 15 minutes. The copy of approved labeling for Zometa® (Zoledronic acid injection), dated 25 May, 06 is provided herewith as Exhibit-4.

II. Determination whether Zometa (Zoledronic acid for Injection) , held by Novartis Pharma is discontinued.

It is known from the Code of Federal Regulations that when an ANDA makes a reference to a discontinued label of a drug, FDA may still approve the ANDA upon determination that the formulation was not withdrawn for reasons of safety or effectiveness (21 U.S.C. Section 355 (j)(6) and 21 CFR §§ 314.122 and 314.161).[1] Similarly FDA is also authorized to approve an ANDA that omits in its labeling an indication or other aspects for the listed drug. The regulation 21 CFR § 314.94(a)(9)(iii)[2] permits ANDA application to seek approval for parenteral products that differ in inactive ingredient. The proposed generic formulation for Zoledronic acid powder for Injection is identical with lyophilized formulation (currently not available in market) of Zometa ®(Zoledronic acid for Injection), in its dosage form and formula.

The proposed generic product is identical with currently marketed Zometa ®(Zoledronic acid Injection) with respect to indication, active ingredient, strength and route of administration.

The petitioner is not aware of any documentation which establish that the lyophilized formulation Zometa ®(Zoledronic acid for Injection) has been discontinued for safety or efficacy reasons.

Proposed generic product:

The proposed generic product's formulation is identical to the lyophilized formulation of Zometa ®(Zoledronic acid for Injection) and is supplied as a freeze-dried powder in a clear glass vial containing Zoledronic acid 4 mg/vial. The formula of proposed generic product, which is subject of this petition, is provided in the following

Table I.

Components	mg/vial
Zoledronic acid monohydrate (equivalent to Zoledronic acid anhydrous)	4.00
Mannitol, USP	220.00
Sodium citrate dihydrate, USP	24.00
Water for Injection, USP	*

* Not present in final product except traces.

[1] Although the regulations are consistent with relief sought, this citizen petition is submitted pursuant to section 505(j)(2)(C) of the Federal Food Drug, and Cosmetic Act ("The FDC Act") and 21 CFR § 314.93.

[2] 21 CFR § 314.94 (a)(9)(iii) : "Inactive ingredient changes permitted in drug products intended for parenteral use". An applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed generic drug product.

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III. Conclusion

For all the reasons stated above in this statement grounds, the petitioner seeks FDA to make a determination that the lyophilized formulation of ZOMETA ®(Zoledronic acid for Injection) was not voluntarily withdrawn by Novartis Pharma for reasons of safety or effectiveness and that the use of that labeling by the proposed generic product would not render the proposed generic product less safe or effective and would be therapeutically equivalent to the currently marketed product, Zometa® (Zoledronic acid injection).

Accordingly, this petition seeks a determination that the lyophilized formulation of ZOMETA ®(Zoledronic acid for Injection) is suitable for submission as an Abbreviated New Drug Application (ANDA).

C. Environmental Impact

This petition is entitled to a categorical exclusion under 21 CFR §§ 25.30 and 25.31

D. Economic Report

The petitioner agrees to provide an economic analysis if requested by the agency.

E. Certification

The undersigned certifies that, 'to the best knowledge and belief of the undersigned, this petition includes all information and review upon which the petitioner relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Exhibit-1 : Copy of letter from Dealer indicating non-availability of lyophilized form of Zometa
Exhibit-1 : Copy of internet Orange book listing for Zometa®
Exhibit-2 : Last Approved labeling (22, Feb,02) for lyophilized Zometa®.
Exhibit-3 : Last Approved labeling (25, May,06) for liquid concentrate Zometa®.

Respectfully submitted,

Dr. Abhay. Muthal.
General Manager, Regulatory Affairs
Sun Pharmaceutical Industries Ltd., India.

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EXHIBIT-1

COLLIE DRUGS INC

21722 HARPER
ST. CLAIR SHORES
MI, 48080
TEL-586-776-7122
FAX-586-776-6551

June 25, 2007

To: Caraco Pharmaceutical Laboratories Ltd.

RE: Zometa 4mg/ml Injection (Zoledronic acid for injection (Lyophilized)) by Norvartis, NDC No: 0078-0350-84

Dear Sir,

This letter is to inform you that upon our telephone conference with the ~~Novaltis~~ Novartis, we were told that the Zometa 4mg/ml Injection (Zoledronic acid for injection (Lyophilized) has been discontinued. However, Zometa 4mg/5ml injection (NDC No: 0078-0387-25) is available.

Thank You,

Sami Shimoon, R.PH

EXHIBIT-2

Active Ingredient Search Results from "OB_Rx" table for query on "zoledronic."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021223		Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOMETA	NOVARTIS
021223		Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/VIAL	ZOMETA	NOVARTIS
021817		Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	RECLAST	NOVARTIS

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through July, 2007
Patent and Generic Drug Product Data Last Updated: September 04, 2007

EXHIBIT-3

Zometa®(zoledronic acid for injection)

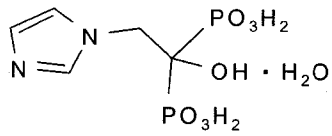
For Intravenous Infusion

Rx only

Prescribing Information

DESCRIPTION

Zometa® contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zoledronic acid is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and its molar mass is 290.1g/Mol. Zoledronic acid is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Zometa® (zoledronic acid for injection) is available in vials as a sterile powder for reconstitution for intravenous infusion. Each vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis .

Inactive Ingredients: mannitol, USP, as bulking agent, and sodium citrate, USP, as buffering agent.

CLINICAL PHARMACOLOGY

General

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

Pharmacokinetics

Distribution

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg Zometa® (zoledronic acid for injection) were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of Cmax 24 hours post infusion with population half-lives of $t_{½\alpha}$ 0.24 hours and $t_{½\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between days 2 and 28 post infusion, and a terminal elimination half-life $t_{½\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC_{0-24h} ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and ex vivo studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 22% and was independent of the concentration of zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases on average (± s.d.) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0 – 24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4 mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 403 ± 118 ng/mL vs 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations

Pharmacokinetic data in patients with hypercalcemia are not available.

Pediatrics: Pharmacokinetic data in pediatric patients are not available.

Geriatrics: The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases who ranged in age from 38 years to 84 years.

Race: The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer and bone metastases.
Hepatic Insufficiency: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Insufficiency: The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately impaired renal function. Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43%. Limited

pharmacokinetic data are available for Zometa in patients with severe renal impairment (creatinine clearance <30 mL/min). Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 ml/min.

Creatinine clearance is calculated by the Cockcroft-Gault formula (Creatinine clearance (CL_{cr}, mL/min)= (140-age)*weight (kg)/X*(plasma creatinine concentration, where X= 72 for males, and X=85 for females). Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa, CL (L/h)=$6.5(CL_{cr}/90)^{0.4}$. These formulae can be used to predict the Zometa AUC in patients. CL = Dose/AUC. The average AUC in patients with normal renal function was 0.42 mg*h/L (%CV 33) following a 4 mg dose of Zometa. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed. (See WARNINGS)

Pharmacodynamics

Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of Zometa are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.

Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) and metastatic bone disease. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Reducing excessive bone resorption and maintaining adequate fluid administration are, therefore, essential to the management of hypercalcemia of malignancy.

Patients who have hypercalcemia of malignancy can generally be divided into two groups according to the pathophysiologic mechanism involved: humoral hypercalcemia and hypercalcemia due to tumor invasion of bone. In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels (corrected serum calcium, CSC) is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see DOSAGE AND ADMINISTRATION).

Clinical Trials in Hypercalcemia of Malignancy

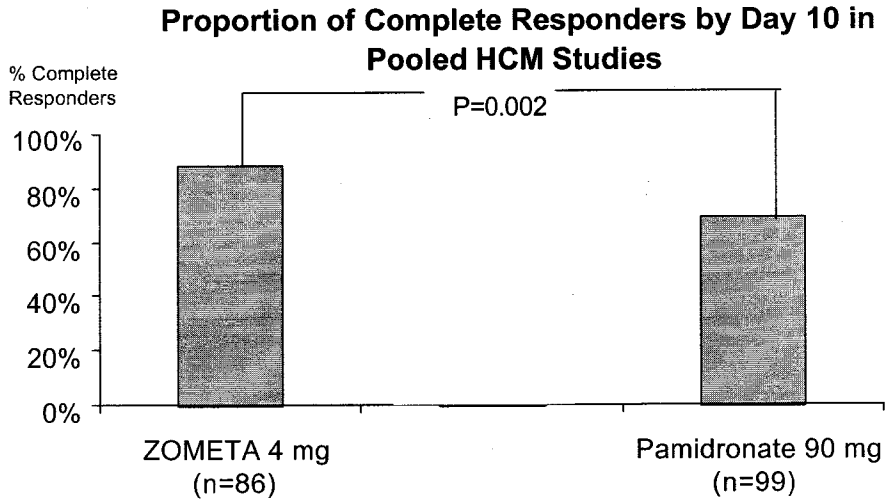
Two identical multicenter, randomized, double-blind, double-dummy studies of Zometa 4 mg given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM). **NOTE: Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes. (See WARNINGS and DOSAGE AND ADMINISTRATION.**) The treatment groups in the clinical studies were generally well balanced with regards to age, sex, race, and tumor types. The mean age of the study population was 59 years; 81% were Caucasian, 15% were

Black, and 4% were of other races. Sixty percent of the patients were male. The most common tumor types were lung, breast, head and neck, and renal.

In these studies, HCM was defined as a corrected serum calcium (CSC) concentration of ≥12.0 mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to ≤ 10.8 mg/dL (2.70 mmol/L) within 10 days after drug infusion.

To assess the effects of Zometa versus those of pamidronate, the two multicenter HCM studies were combined in a pre-planned analysis. The results of the primary analysis revealed that the proportion of patients that had normalization of corrected serum calcium by Day 10 were 88% and 70% for Zometa 4 mg and pamidronate 90 mg, respectively (p=0.002). (see Figure 1) **In these studies, no additional benefit was seen for Zometa 8 mg over Zometa 4 mg; however, the risk of renal toxicity of Zometa 8 mg was significantly greater than that seen with Zometa 4 mg.**

Figure 1



Secondary efficacy variables from the pooled HCM studies included the proportion of patients who had normalization of corrected serum calcium (CSC) by Day 4; the proportion of patients who had normalization of CSC by Day 7; time to relapse of HCM; and duration of complete response. Time to relapse of HCM was defined as the duration (in days) of normalization of serum calcium from study drug infusion until the last CSC value <11.6 mg/dL (<2.90 mmol/L). Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC ≤ 10.8 mg/dL (2.70 mmol/L). The results of these secondary analyses for Zometa 4 mg and pamidronate 90 mg are shown in Table 1.

Table 1. Secondary Efficacy Variables in Pooled HCM Studies

	Zometa® 4mg		**Pamidronate 90mg**	
Complete response	N	Response rate	N	Response rate
By Day 4	86	45.3%	99	33.3%
By Day 7	86	82.6%*	99	63.6%
Duration of response	N	Median duration (days)	N	Median duration (days)
Time to relapse	86	30*	99	17
Duration of complete response	76	32	69	18

*P less than 0.05 vs. pamidronate 90 mg

Clinical Trials in Multiple Myeloma and Bone Metastases of Solid Tumors

Table 2 describes three randomized Zometa trials in patients with multiple myeloma and bone metastases of solid tumors. These include a pamidronate-controlled study in breast cancer and multiple myeloma, a placebo-controlled study in prostate cancer and a placebo-controlled study in other solid tumors. The prostate cancer study required documentation of previous bone metastases and 3 consecutive rising PSAs while on hormonal therapy. The other placebo-controlled solid tumor study included patients with bone metastases from malignancies other than breast cancer and prostate cancer, listed in Table 3.

Table 2: Overview of Phase III studies

Study No.	No. of Patients	Treatment Duration	Zometa® dose	Control	Patient population
010	1648	12 months	4 and 8* mg Q3 - 4weeks	Pamidronate 90 mg Q3 - 4 weeks	Multiple myeloma or metastatic breast cancer
039	643	15 months	4 and 8* mg Q3 weeks	Placebo	Metastatic prostate cancer
011	773	9 months	4 and 8* mg Q3 weeks	Placebo	Metastatic solid tumor other than breast or prostate cancer

* Patients who were randomized to the 8 mg Zometa group are not included in any of the analyses in this package insert.

Table 3: Solid Tumor Patients by cancer type and treatment arm

Cancer type	Zometa® 4 mg N	Placebo N
NSCLC	124	121
Renal	26	19
Small cell lung cancer	19	22
Colorectal	19	16
Unknown	17	14
Bladder	11	16
GI (other)	10	12
Head and neck	6	4
Genitourinary	6	6
Malignant melanoma	5	4
Hepatobiliary	3	4
Thyroid	2	4
Other	3	2
Sarcoma	3	3
Neuroendocrine/carcinoid	2	3
Mesothelioma	1	0

The planned duration of therapy was 12 months for multiple myeloma and breast cancer, 15 months for prostate cancer, and 9 months for the other solid tumors.

The studies were amended twice because of renal toxicity. The Zometa infusion duration was increased from 5 minutes to 15 minutes. After all patients had been accrued, but while dosing and follow-up continued, patients in the 8 mg Zometa treatment arm were switched to 4 mg. Patients who were randomized to the Zometa 8 mg group are not included in these analyses.

Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in antineoplastic therapy due to increased pain was an SRE in the prostate cancer study only. Planned analyses included the proportion of patients with an SRE during the study (the primary endpoint) and time to first SRE. Results for the two Zometa placebo-controlled studies are given in Table 4.

Table 4. Zometa compared to placebo in patients with bone metastases from prostate cancer or other solid tumors

Study	Study Arm	Analysis of proportion of patients with an SRE*			Analysis of time to first SRE*			
		Proportion	Difference & 95% CI	P value	Median (days)	HR	95% CI of HR	P value
Prostate Cancer	Zol 4mg	33%	-11 (-20, -2)	0.021	NR	0.67	(0.49, 0.91)	0.011
	Placebo	44%	—	—	321	—	—	—
Solid Tumors	Zol 4mg	38%	-7 (-15, 2)	0.13	230	0.73	(0.55, 0.96)	0.023
	Placebo	44%	—	—	163	—	—	—

*SRE = Skeletal Related Event
NR = Not reached by 420 days
HR = Hazard Ratio

In the breast cancer and myeloma trial, efficacy was determined by a non-inferiority analysis comparing Zometa to pamidronate 90 mg for the proportion of patients with an SRE. This analysis required an estimation of pamidronate efficacy. Historical data from 1128 patients in three pamidronate placebo-controlled trials demonstrated that pamidronate decreased the proportion of patients with an SRE by 13.1% (95% CI = 7.3%,18.9%). Results of the comparison of treatment with Zometa compared to pamidronate are given in Table 5.

Table 5. Zometa compared to pamidronate in patients with multiple myeloma or bone metastases from Breast Cancer

Study	Study Arm	Analysis of proportion of patients with an SRE*			Analysis of time to first SRE*			
		Proportion	Difference & 95% CI	P value	Median (days)	HR	95% CI of HR	P value
Multiple Myeloma and Breast Cancer	Zol 4mg	44%	-2 (-7.9, 3.7)	0.46	373	0.92	(0.77,1.09)	0.322
	Pamidronate 90 mg	46%	---	---	363	---	---	---

*SRE = Skeletal Related Event
HR = Hazard Ratio

INDICATIONS AND USAGE
Hypercalcemia of Malignancy

Zometa® (zoledronic acid for injection) is indicated for the treatment of hypercalcemia of malignancy.

Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia. The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

Multiple Myeloma and Bone Metastases of Solid Tumors

Zometa is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy

CONTRAINDICATIONS

Zometa® (zoledronic acid for injection) is contraindicated in patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of Zometa.

WARNINGS

DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOMETA ® SHOULD NOT EXCEED 4 MG AND THE DURATION OF INFUSION SHOULD BE NO LESS THAN 15 MINUTES.

BECAUSE SAFETY AND PHARMACOKINETIC DATA ARE LIMITED IN PATIENTS WITH SEVERE RENAL IMPAIRMENT:

- **ZOMETA TREATMENT IS NOT RECOMMENDED IN PATIENTS WITH BONE METASTASES WITH SEVERE RENAL IMPAIRMENT.** In the clinical studies, patients with serum creatinine > 3.0 mg/dl were excluded.
- **ZOMETA TREATMENT IN PATIENTS WITH HYPERCALCEMIA OF MALIGNANCY SHOULD BE CONSIDERED ONLY AFTER EVALUATING THE RISKS AND BENEFITS OF TREATMENT.** In the clinical studies, patients with serum creatinine > 400 umol/l or > 4.5 mg/dl were excluded.

Bisphosphonates, including Zometa (zoledronic acid for injection), have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. In clinical trials, the risk for renal function deterioration (defined as an increase in serum creatinine) was significantly increased in patients who received Zometa over 5 minutes compared to patients who received the same dose over 15 minutes. In addition, the risk for renal function deterioration and renal failure was significantly increased in patients who received Zometa 8 mg, even when given over 15 minutes. While this risk is reduced with the Zometa 4 mg dose administered over 15 minutes, deterioration in renal function can still occur. Risk factors for this deterioration include elevated baseline creatinine and multiple cycles of treatment with the bisphosphonate.

Patients who receive Zometa should have serum creatinine assessed prior to each treatment. Patients treated with Zometa for bone metastases should have the dose withheld if renal function has deteriorated. (See DOSAGE AND ADMINISTRATION). Patients with hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk.

PREGNANCY: ZOMETA SHOULD NOT BE USED DURING PREGNANCY. Zometa may cause fetal harm when administered to a pregnant woman. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure (an i.v. dose of 4 mg based on an AUC comparison) resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations (See PRECAUTIONS, Pregnancy Category D).

There are no studies in pregnant women using Zometa. I f the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zometa® (zoledronic acid for injection). If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zometa. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zometa in order to avoid hypocalcemia. Zometa should be used with caution with other nephrotoxic drugs.

Renal Insufficiency:

Limited clinical data are available regarding use of Zometa in patients with renal impairment. Zometa is excreted primarily via the intact kidney and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Serum creatinine should be monitored in all patients treated with Zometa prior to each dose.

Studies of Zometa in the treatment of hypercalcemia of malignancy excluded patients with serum creatinine $\geq$ 400 µmol/L or $\geq$ 4.5 mg/dL. Bone metastasis trials excluded patients with serum creatinine > 265 µmol/L or > 3.0 mg/ dL. No clinical or pharmacokinetics data are available to guide dose selection or to provide guidance on how to safely use Zometa in patients with severe renal impairment. For hypercalcemia of malignancy, Zometa should be used in patients with severe renal impairment only if the expected clinical benefits outweigh the risk of renal failure and after considering other available treatment options. (See WARNINGS.) Dose adjustments of Zometa are not necessary in treating patients for hypercalcemia presenting with mild to moderate renal impairment prior to initiation of therapy (serum creatinine < 400 µmol/L or < 4.5 mg/dL. For bone metastases, the use of Zometa in patients with severe renal impairment is not recommended. In studies of patients with bone metastases, patients with a serum creatinine >3.0 mg/dL were excluded.

Patients receiving Zometa for hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated and consideration should be given as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk. In patients receiving Zometa for bone metastases, who show evidence of deterioration in renal function, Zometa treatment should be withheld until renal function returns to baseline (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency:

Only limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use Zometa in these patients.

Patients with Asthma:

While not observed in clinical trials with Zometa, administration of other bisphosphonates has been associated with bronchoconstriction in aspirin-sensitive asthmatic patients. Zometa should be used with caution in patients with aspirin-sensitive asthma.

Laboratory Tests

Serum creatinine should be monitored prior to each dose of Zometa. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly. (See WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS.)

Drug Interactions

In vitro studies indicate that zoledronic acid is approximately 56% bound to plasma proteins. *In vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug. However, no *in vivo* drug interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This has not been reported in Zometa clinical trials. Caution should also be exercised when Zometa is used in combination with loop diuretics due to an increased risk of hypocalcemia. Caution is indicated when Zometa is used with other potentially nephrotoxic drugs.

In multiple myeloma patients, the risk of renal dysfunction may be increased when Zometa is used in combination with thalidomide.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥ 0.002 times a human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≤ 0.2 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas).

Mutagenesis: Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus assay.

Impairment of Fertility: Female rats were given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group (with systemic exposure of 0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and high–dose group included an increase in preimplantation losses and a decrease in the number of implantations and live fetuses.

Pregnancy Category D *See WARNINGS.*

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (≥ 0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (with a systemic exposure of ≥ 0.07 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given a subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg/day during gestation, adverse fetal effects were observed in the mid- and high-dose groups (with systemic exposures of 2.4 and 4.8 times, respectively, the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of

4 mg, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (≤ 0.5 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas), no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses ≥ 0.05 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Adverse maternal effects were associated with, and may have been caused by, drug–induced hypocalcemia.

Nursing Mothers

It is not known whether Zometa is excreted in human milk. Because many drugs are excreted in human milk, and because Zometa binds to bone long-term, Zometa should not be administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Zometa in pediatric patients have not been established. Because of long-term retention in bone, Zometa should only be used in children if the potential benefit outweighs the potential risk.

Geriatric Use

Clinical studies of Zometa in hypercalcemia of malignancy included 34 patients who were 65 years of age or older No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zometa as compared to younger patients. Controlled clinical studies of Zometa in the treatment of multiple myeloma and bone metastases of solid tumors in patients over age 65 revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

ADVERSE REACTIONS

Hypercalcemia of malignancy

Adverse reactions to Zometa® (zoledronic acid for injection) are usually mild and transient and similar to those reported for other bisphosphonates. Intravenous administration has been most commonly associated with fever. Occasionally, patients experience a flu-like syndrome consisting of fever, chills, bone pain and/or arthralgias, and myalgias. Gastrointestinal reactions such as nausea and vomiting have been reported following intravenous infusion of Zometa. Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Rare cases of rash, pruritus, and chest pain have been reported following treatment with Zometa.

As with other bisphosphonates, cases of conjunctivitis and hypomagnesemia have been reported following treatment with Zometa.

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in two clinical trials of Zometa in patients with HCM are shown in Table 6.

Table 6: Grade 3-4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials in Patients with HCM

	Grade 3				Grade 4			
Laboratory Parameter	**Zometa® 4 mg**		**Pamidronate 90 mg**		**Zometa® 4 mg**		**Pamidronate 90 mg**	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine[1]	2/86	(2.3%)	3/100	(3.0%)	0/86	--	1/100	(1.0%)
Hypocalcemia[2]	1/86	(1.2%)	2/100	(2.0%)	0/86	--	0/100	--
Hypophosphatemia[3]	36/70	(51.4%)	27/81	(33.3%)	1/70	(1.4%)	4/81	(4.9%)
Hypomagnesemia[4]	0/71	--	0/84	--	0/71	--	1/84	(1.2%)

[1] Grade 3 (>3xUpper limit of Normal); Grade 4 (>6xUpper limit of Normal)
[2] Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3] Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4] Grade 3 (<0.8 mEq/L); Grade 4 (<0.5 mEq/L)

Table 7 provides adverse events that were reported by 10% or more of the 189 patients treated with Zometa 4 mg or pamidronate 90 mg from the two controlled multi-center HCM trials. Adverse events are listed regardless of presumed causality to study drug.

Table 7: Percentage of Patients with Adverse Events □ 10% Reported in Hypercalcemia of Malignancy Clinical Trials By Body System

	Zometa® 4 mg n (%)	Pamidronate 90 mg n (%)
Patients Studied		
Total no. of patients studied	86 (100)	103 (100)
Total no. of patients with any AE	81 (94.2)	95 (92.2)
Body as a Whole		
Fever	38 (44.2)	34 (33.0)
Progression of Cancer	14 (16.3)	21 (20.4)
Digestive		
Nausea	25 (29.1)	28 (27.2)
Constipation	23 (26.7)	13 (12.6)
Diarrhea	15 (17.4)	17 (16.5)
Abdominal Pain	14 (16.3)	13 (12.6)
Vomiting	12 (14.0)	17 (16.5)
Anorexia	8 (9.3)	14 (13.6)
Cardiovascular		
Hypotension	9 (10.5)	2 (1.9)
Hemic and Lymphatic System		
Anemia	19 (22.1)	18 (17.5)
Infections		
Moniliasis	10 (11.6)	4 (3.9)
Laboratory Abnormalities		
Hypophosphatemia	11 (12.8)	2 (1.9)
Hypokalemia	10 (11.6)	16 (15.5)
Hypomagnesemia	9 (10.5)	5 (4.9)
Musculoskeletal		
Skeletal Pain	10 (11.6)	10 (9.7)
Nervous		
Insomnia	13 (15.1)	10 (9.7)
Anxiety	12 (14.0)	8 (7.8)
Confusion	11 (12.8)	13 (12.6)
Agitation	11 (12.8)	8 (7.8)
Respiratory		
Dyspnea	19 (22.1)	20 (19.4)
Coughing	10 (11.6)	12 (11.7)
Urogenital		
Urinary Tract Infection	12 (14.0)	15 (14.6)

The following adverse events from the two controlled multi-center HCM trials (n=189) were reported by a greater percentage of patients treated with Zometa 4 mg than with pamidronate 90 mg and occurred with a frequency of greater than or equal to 5% but less than 10%. Adverse events are listed regardless of presumed causality to study drug.

Body as a Whole: asthenia, chest pain, leg edema, mucositis, metastases

Digestive System: dysphagia

Hemic and Lymphatic System: granulocytopenia, thrombocytopenia, pancytopenia

Infection: non-specific infection

Laboratory Abnormalities: hypocalcemia

Metabolic and Nutritional: dehydration

Musculoskeletal: arthralgias

Nervous System: headache, somnolence

Respiratory System: pleural effusion

NOTE: In the HCM clinical trials, pamidronate 90 mg was given as a 2-hour intravenous infusion. The relative safety of pamidronate 90 mg given as a 2-hour intravenous infusion compared to the same dose given as a 24-hour intravenous infusion has not been adequately studied in controlled clinical trials.

Multiple Myeloma and Bone Metastases of Solid Tumors

Table 8 provides adverse events that were reported by 10% or more of the 2185 patients treated with Zometa 4 mg, pamidronate 90 mg or placebo from the four controlled multi-center Bone Metastases trials. Adverse events are listed regardless of presumed causality to study drug.

Table 8: Percentage of Patients with Adverse Events □ 10% Reported in Four Bone Metastases Clinical Trials By Body System

	Zometa® 4 mg n (%)	Pamidronate 90 mg n (%)	Placebo n (%)
Patients Studied			
Total no. of patients	1099 (100)	631 (100)	455 (100)
Total no. of patients with any AE	1081 (98)	622 (99)	444 (98)
Blood and lymphatic			
Anemia NOS	320 (29)	170 (27)	119 (26)
Neutropenia	121 (11)	87 (14)	34 (8)
Gastrointestinal			
Nausea	470 (43)	282 (45)	160 (35)
Vomiting NOS	328 (30)	189 (30)	114 (25)
Constipation	307 (28)	148 (24)	161 (35)
Diarrhea NOS	238 (22)	157 (25)	76 (17)
Abdominal pain NOS	128 (12)	70 (11)	43 (10)
General disorders and administration site			
Fatigue	394 (36)	235 (37)	125 (28)
Pyrexia	326 (30)	175 (28)	83 (18)
Weakness	232 (21)	103 (16)	105 (23)
Oedema lower limb	203 (19)	115 (18)	76 (17)
Rigors	107 (10)	64 (10)	21 (5)
Infections			
Urinary tract infection NOS	115 (11)	53 (8)	39 (9)
Upper respiratory tract infection NOS	88 (8)	83 (13)	26 (6)
Metabolism			
Anorexia	220 (20)	76 (12)	98 (22)
Weight decreased	143 (13)	45 (7)	57 (13)

	Zometa® 4 mg n (%)	Pamidronate 90 mg n (%)	Placebo n (%)
Dehydration	135 (12)	57 (9)	54 (12)
Appetite decreased NOS	119 (11)	46 (7)	39 (9)
Musculoskeletal			
Bone pain	579 (53)	345 (55)	272 (60)
Myalgia	232 (21)	148 (24)	68 (15)
Arthralgia	195 (18)	109 (17)	60 (13)
Back pain	113 (10)	79 (13)	29 (6)
Neoplasms			
Malignant neoplasm aggravated	166 (15)	71 (11)	72 (16)
Nervous			
Headache NOS	193 (18)	152 (24)	47 (10)
Dizziness (excluding vertigo)	158 (14)	79 (13)	52 (11)
Insomnia NEC	154 (14)	106 (17)	67 (15)
Paraesthesia NEC	129 (18)	85 (14)	28 (6)
Hypoaesthesia	109 (10)	63 (10)	38 (8)
Psychiatric			
Depression NEC	136 (12)	89 (14)	41 (9)
Anxiety NEC	101 (9)	76 (12)	34 (8)
Respiratory			
Dyspnoea NOS	264 (24)	147 (23.)	93 (20)
Cough	212 (19)	132 (21)	57 (13)
Skin			
Alopecia	119 (11)	83 (13)	30 (7)
Dermatitis NOS	108 (10)	68 (11)	35 (8)

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorous, and serum magnesium observed in four clinical trials of Zometa in patients with Bone Metastases are shown in Tables 9 and 10.

Table 9: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Four Clinical Trials in Patients with Bone Metastases

	Grade 3					
Laboratory Parameter	**Zometa® 4 mg**		**Pamidronate 90 mg**		**Placebo**	
	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine[1*]	7/529	(1.3%)	4/268	(1.5%)	2/241	(0.8%)
Hypocalcemia[2]	7/1041	(0.7%)	4/610	(0.7%)	0/415	--
Hypophosphatemia[3]	96/1041	(9.2%)	40/611	(6.6%)	13/415	(3.1%)
Hypermagnesemia[4]	19/1039	(1.8%)	3/609	(0.5%)	8/415	(1.9%)
Hypomagnesemia[5]	0/1039	--	0/609	--	1/415	(0.2%)

[1] Grade 3 (>3xUpper limit of Normal); Grade 4 (>6xUpper limit of Normal)
[*] Serum creatinine data for all patients randomized after the 15 minute infusion amendment
[2] Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3] Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4] Grade 3 (>3 mEq/L); Grade 4 (>8 mEq/L)
[5] Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Table 10: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Four Clinical Trials In Patients with Bone Metastases.

	Grade 4					
Laboratory Parameter	**Zometa® 4 mg**		**Pamidronate 90 mg**		**Placebo**	
	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine[1*]	2/529	(0.4%)	1/268	(0.4%)	0/241	--
Hypocalcemia[2]	6/1041	(0.6%)	2/610	(0.3%)	1/415	(0.2%)
Hypophosphatemia[3]	6/1041	(0.6%)	0/611	--	1/415	(0.2%)
Hypermagnesemia[4]	0/1039	--	0/609	--	2/415	(0.5%)
Hypomagnesemia[5]	2/1039	(0.2%)	2/609	(0.3%)	0/415	--

[1] Grade 3 (>3xUpper limit of Normal); Grade 4 (>6xUpper limit of Normal)
[*] Serum creatinine data for all patients randomized after the 15 minute infusion
[2] Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3] Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4] Grade 3 (>3 mEq/L); Grade 4 (>8 mEq/L)
[5] Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Among the less frequently occurring adverse events (< 15% of patients), rigors, hypokalemia, influenza-like illness, and hypocalcemia showed a trend for more events with bisphosphonate administration (Zometa 4 mg and pamidronate groups) compared to the placebo group.

Less common adverse events reported more often with Zometa 4 mg than pamidronate included decreased weight, which was reported in 13.0% of patients in the Zometa 4 mg compared with 7.1% in the pamidronate group. The incidence of decreased weight, however, was similar for the placebo group (12.5%) and Zometa. Decreased appetite was reported in slightly more patients in the Zometa 4 mg (10.8%) compared with the pamidronate (7.3%) and placebo (8.6%) groups, but the clinical significance of these small differences is not clear.

Renal toxicity

In the bone metastases trials renal deterioration was defined as an increase of 0.5 mg/dL for patients with normal baseline creatinine (<1.4 mg/dL) or an increase of 1.0 mg/dL for patients with an abnormal baseline creatinine (□1.4 mg/dL). The following are data on the incidence of renal deterioration in patients receiving Zometa 4 mg over 15 minutes in these trials. See Table 11.

Table 11: Percentage of patients with renal function deterioration who were randomized following the 15-minute infusion amendment

Patient Population/Baseline creatinine		
Multiple Myeloma and Breast Cancer		
	Zometa® 4mg n/N (%)	Pamidronate 90 mg n/N (%)
Normal	23/246 (9.3%)	20/246 (8.1%)
Abnormal	1/26 (3.8%)	2/22 (9.1%)
Total	24/272 (8.8%)	22/268 (8.2%)
Solid Tumors		
	Zometa® 4mg n/N (%)	Placebo n/N (%)
Normal	17/154 (11%)	10/143 (7%)
Abnormal	1/11 (9.1%)	1/20 (5%)
Total	18/165 (10.9%)	11/163 (6.7%)
Prostate Cancer		
	Zometa® 4mg n/N (%)	Placebo n/N (%)
Normal	10/82 (12.2%)	7/68 (10.3%)
Abnormal	4/10 (40%)	2/10 (20%)
Total	14/92 (15.2%)	9/78 (11.5%)

The risk of deterioration in renal function appeared to be related to time on study, whether patients were receiving Zometa (4 mg over 15 minutes), placebo, or pamidronate.

OVERDOSAGE

There is no experience of acute overdose with Zometa® (zoledronic acid for injection). Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

In controlled clinical trials, administration of Zometa 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15-minute intravenous infusion. In controlled clinical trials, Zometa 8 mg has been shown to be associated with an increased risk of renal toxicity compared to Zometa 4 mg, even when given as a 15-minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy. **Single doses of Zometa should not exceed 4 mg and the duration of the intravenous infusion should be no less than 15 minutes. (See WARNINGS.)**

DOSAGE AND ADMINISTRATION

Hypercalcemia of malignancy

Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Zometa® (zoledronic acid for injection). Vigorous saline hydration alone may be sufficient to treat mild, asymptomatic hypercalcemia.

The maximum recommended dose of Zometa in hypercalcemia of malignancy (albumin-corrected serum calcium* $\geq$12 mg/dL (3.0 mmol/L)) is 4 mg. The 4 mg dose must be given as a single-dose intravenous infusion over **no less than 15 minutes**.

Patients should be adequately rehydrated prior to administration of Zometa. (See WARNINGS and PRECAUTIONS.)

Retreatment with Zometa 4 mg, may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zometa and possible deterioration in renal function must be assessed prior to retreatment with Zometa (See WARNINGS and PRECAUTIONS.)

*Albumin-corrected serum calcium (Cca, mg/dL) = Ca + 0.8 (mid-range albumin-measured albumin in mg/dL).

Multiple myeloma and metastatic bone lesions from solid tumors

The recommended dose of Zometa in patients with multiple myeloma and metastatic bone lesions from solid tumors is 4 mg infused over 15 minutes every three or four weeks. Duration of treatment in the clinical studies was 15 months for prostate cancer, 12 months for breast cancer and multiple myeloma, and 9 months for other solid tumors. Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

Serum creatinine should be measured before each Zometa dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dL
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dL.

In the clinical studies, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value.

Preparation of Solution

Zometa is reconstituted by adding 5 mL of Sterile Water for Injection, USP, to each vial. The resulting solution allows for withdrawal of 4 mg of zoledronic acid. The drug must be completely dissolved before the solution is withdrawn.

The maximum recommended 4 mg-dose must be further diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. The dose must be given as a single intravenous infusion over no less than 15 minutes.

If not used immediately after reconstitution, for microbiological integrity, the solution should be refrigerated at 36°- 46°F (2-8°C). The total time between reconstitution, dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

Zometa must not be mixed with calcium-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs.

Method of Administration

DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOMETA SHOULD NOT EXCEED 4 MG AND THE DURATION OF INFUSION SHOULD BE NO LESS THAN 15 MINUTES. (SEE WARNINGS)

There must be strict adherence to the intravenous administration recommendations for Zometa in order to decrease the risk of deterioration in renal function.

Note: **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

HOW SUPPLIED

Each vial contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP and 24 mg of sodium citrate, USP.

Carton of 1 vial NDC 0078-0350-84

Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F)

Manufactured by Novartis Pharma AG Basle, Switzerland

For Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936

EXHIBIT-4

NOVARTIS

T2005-72

Zometa®
(zoledronic acid) Injection

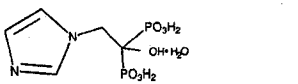
Concentrate for Intravenous Infusion

Rx only

Prescribing Information

DESCRIPTION

Zometa® contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zoledronic acid is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and its molar mass is 290.1g/Mol. Zoledronic acid is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Zometa® (zoledronic acid) Injection is available in vials as a sterile liquid concentrate solution for intravenous infusion. Each 5-mL vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis.

Inactive Ingredients: mannitol, USP, as bulking agent, water for injection and sodium citrate, USP, as buffering agent.

CLINICAL PHARMACOLOGY

General

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

Pharmacokinetics

Distribution

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg Zometa® were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2\alpha}$, 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC_{0-24h} ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 22% and was independent of the concentration of zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases on average (± s.d.) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ((mean ± SD) 403 ± 118 ng/mL vs 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs 420 ± 216 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations

Pharmacokinetic data in patients with hypercalcemia are not available.

Pediatrics: Pharmacokinetic data in pediatric patients are not available.

Geriatrics: The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases who ranged in age from 38 years to 84 years.

Race: The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer and bone metastases.

Hepatic Insufficiency: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Insufficiency: The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately-impaired renal function. Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data are available for Zometa in patients with severe renal impairment (creatinine clearance <30 mL/min). Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 mL/min. Creatinine clearance is calculated by the Cockcroft-Gault formula:

$$CrCl = \frac{(140 - \text{age (years)}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa, CL (L/h)=6.5(CL_{cr}/90)$^{0.4}$. These formulae can be used to predict the Zometa AUC in patients, where CL = Dose/$AUC_{0-\infty}$. The average AUC_{0-24} in patients with normal renal function was 0.42 mg•h/L and the calculated $AUC_{0-\infty}$ for a patient with creatinine clearance of 75 mL/min was 0.66 mg•h/L following a 4-mg dose of Zometa. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed. (See WARNINGS.)

Pharmacodynamics

Hypercalcemia of Malignancy

Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of Zometa are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) and metastatic bone disease. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Reducing excessive bone resorption and maintaining adequate fluid administration are, therefore, essential to the management of hypercalcemia of malignancy.

Patients who have hypercalcemia of malignancy can generally be divided into two groups according to the pathophysiologic mechanism involved: humoral hypercalcemia and hypercalcemia due to tumor invasion of bone. In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally-mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels (corrected serum calcium, CSC) is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see DOSAGE AND ADMINISTRATION).

CLINICAL STUDIES

Clinical Trials in Hypercalcemia of Malignancy

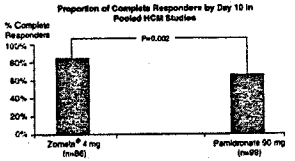
Two identical multicenter, randomized, double-blind, double-dummy studies of Zometa given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM). **NOTE: Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes. (See WARNINGS and DOSAGE AND ADMINISTRATION.)** The treatment groups in the clinical studies were generally well balanced with regards to age, sex, race, and tumor types. The mean age of the study population was 59 years; 81% were Caucasian, 15% were Black, and 4% were of other races. Sixty percent of the patients were male. The most common tumor types were lung, breast, head and neck, and renal.

In these studies, HCM was defined as a corrected serum calcium (CSC) concentration of ≥12.0 mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to ≤10.8 mg/dL (2.70 mmol/L) within 10 days after drug infusion.

To assess the effects of Zometa versus those of pamidronate, the two multicenter HCM studies were combined in a pre-planned analysis. The results of the primary analysis revealed that the proportion of patients that had normalization of corrected serum calcium by Day 10 were 88% and 70% for Zometa 4 mg and pamidronate 90 mg, respectively (P=0.002). (See Figure 1.) **In these studies, no additional benefit was seen for Zometa 8 mg over Zometa 4 mg; however, the risk of renal toxicity of Zometa 8 mg was significantly greater than that seen with Zometa 4 mg.**

Figure 1

Proportion of Complete Responders by Day 10 in Pooled HCM Studies



Secondary efficacy variables from the pooled HCM studies included the proportion of patients who had normalization of corrected serum calcium (CSC) by Day 4; the proportion of patients who had normalization of CSC by Day 7; time to relapse of HCM; and duration of complete response. Time to relapse of HCM was defined as the duration (in days) of normalization of serum calcium from study drug infusion until the last CSC value <11.6 mg/dL (<2.90 mmol/L). Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC ≥10.8 mg/dL (2.70 mmol/L). The results of these secondary analyses for Zometa 4 mg and pamidronate 90 mg are shown in Table 1.

Table 1: Secondary Efficacy Variables in Pooled HCM Studies

	Zometa® 4 mg		Pamidronate 90 mg	
Complete Response	**N**	**Response Rate**	**N**	**Response Rate**
By Day 4	86	45.3%	99	33.3%
By Day 7	86	82.6%*	99	63.6%
Duration of Response	**N**	**Median Duration (Days)**	**N**	**Median Duration (Days)**
Time to Relapse	86	30*	99	17
Duration of Complete Response	76	32	69	19

* P less than 0.05 vs. pamidronate 90 mg.

Clinical Trials in Multiple Myeloma and Bone Metastases of Solid Tumors

Table 2 describes an overview of the efficacy population in three randomized Zometa trials in patients with multiple myeloma and bone metastases of solid tumors. These trials included a pamidronate-controlled study in breast cancer and multiple myeloma, a placebo-controlled study in prostate cancer and a placebo-controlled study in other solid tumors. The prostate cancer study required documentation of previous bone metastases and 3 consecutive rising PSAs while on hormonal therapy. The other placebo-controlled solid tumor study included patients with bone metastases from malignancies other than breast cancer and prostate cancer, listed in Table 3. These trials were comprised of a core phase and an extension phase. In trials 010 and 011, only the core phase was evaluated for efficacy as a high percentage of patients did not choose to participate in the extension phase. In study 039, both the core and extension phases were evaluated for efficacy showing the Zometa advantage during the first 15 months was maintained without decrement or improvement for 24 months. The design of the clinical trials 010, 011, and 039 does not permit assessment of whether more than one year administration of Zometa is beneficial. The optimal duration of Zometa administration is not known.

Table 2: Overview of Efficacy Population for Phase III Studies (Core Phase)

Study No.	No. of Patients	Median Duration (Planned Duration) Zometa® 4 mg	Zometa® Dose	Control	Patient Population
010	1,648	12.0 months (13 months)	4 and 8* mg Q3-4 weeks	Pamidronate 90 mg Q3-4 weeks	Multiple myeloma or metastatic breast cancer
039	643	10.5 months (15 months)	4 and 8* mg Q3 weeks	Placebo	Metastatic prostate cancer
011	773	3.8 months (9 months)	4 and 8* mg Q3 weeks	Placebo	Metastatic solid tumor other than breast or prostate cancer

* Patients who were randomized to the 8-mg Zometa group are not included in any of the analyses in this package insert.

Table 3: Solid Tumor Patients by Cancer Type and Treatment Arm

Cancer Type	Zometa® 4 mg N	Placebo N
NSCLC	124	121
Renal	26	19
Small Cell Lung	19	22
Colorectal	19	16
Unknown	17	14
Bladder	11	16
GI (Other)	10	12
Head and Neck	6	4
Genitourinary	6	6
Malignant Melanoma	5	4
Hepatobiliary	3	4

Patients evaluable for efficacy were treated with Zometa for a median duration of 12.0 months for multiple myeloma and breast cancer, 10.5 months for prostate cancer, and 3.8 months for the other solid tumors. The studies were amended twice because of renal toxicity. The Zometa infusion duration was increased from 5 minutes to 15 minutes. After all patients had been accrued, but while dosing and follow-up continued, patients in the 8-mg Zometa treatment arm were switched to 4 mg. Patients who were randomized to the Zometa 8-mg group are not included in these analyses.

Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in antineoplastic therapy due to increased pain was a SRE in the prostate cancer study only. Planned analyses included the proportion of patients with a SRE during the study (the primary endpoint) and time to first SRE. Results for the two Zometa placebo-controlled studies are given in Table 4.

Table 4: Zometa® Compared to Placebo in Patients with Bone Metastases from Prostate Cancer or Other Solid Tumors

		I. Analysis of Proportion of Patients with a SRE[1]			II. Analysis of Time to the First SRE		
Study	Study Arm & Patient Number	Proportion	Difference[2] & 95% CI	P-value	Median (Days)	Hazard Ratio[3] & 95% CI	P-value
Prostate Cancer	Zometa 4 mg (n=214)	33%	-11% (-20%, -1%)	0.02	NR	0.67 (0.49, 0.91)	0.011
	Placebo (n=208)	44%			321		
Solid Tumors	Zometa 4 mg (n=257)	38%	-7% (-15%, 2%)	0.13	230	0.73 (0.55, 0.96)	0.023
	Placebo (n=250)	44%			163		

[1]SRE=Skeletal-Related Event
[2]Difference for the proportion of patients with a SRE of Zometa 4 mg versus placebo.
[3]Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus placebo.

In the breast cancer and myeloma trial, efficacy was determined by a non-inferiority analysis comparing Zometa to pamidronate 90 mg for the proportion of patients with a SRE. This analysis required an estimation of pamidronate efficacy. Historical data from 1,128 patients in three pamidronate placebo-controlled trials demonstrated that pamidronate decreased the proportion of patients with a SRE by 13.1% (95% CI=7.3%,18.9%). Results of the comparison of treatment with Zometa compared to pamidronate are given in Table 5.

Table 5: Zometa® Compared to Pamidronate in Patients with Multiple Myeloma or Bone Metastases from Breast Cancer

		I. Analysis of Proportion of Patients with a SRE[1]			II. Analysis of Time to the First SRE		
Study	Study Arm & Patient Number	Proportion	Difference[2] & 95% CI	P-value	Median (Days)	Hazard Ratio[3] & 95% CI	P-value
Multiple Myeloma & Breast Cancer	Zometa 4 mg (n=561)	44%	-2% (-7.9%, 3.7%)	0.46	373	0.92 (0.77, 1.09)	0.32
	Pamidronate 90 mg (n=555)	46%			363		

[1]SRE=Skeletal-Related Event
[2]Difference for the proportion of patients with a SRE of Zometa 4 mg versus pamidronate 90 mg.
[3]Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus pamidronate 90 mg.

INDICATIONS AND USAGE

Hypercalcemia of Malignancy

Zometa (zoledronic acid) Injection is indicated for the treatment of hypercalcemia of malignancy.

Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia. The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

Multiple Myeloma and Bone Metastases of Solid Tumors

Zometa is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

CONTRAINDICATIONS

Zometa® (zoledronic acid) Injection is contraindicated in patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of Zometa.

WARNINGS

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Zometa® (zoledronic acid) should not exceed 4 mg and the duration of infusion should be no less than 15 minutes. In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zometa dose.

SAFETY AND PHARMACOKINETIC DATA ARE LIMITED IN PATIENTS WITH SEVERE RENAL IMPAIRMENT AND THE RISK OF RENAL DETERIORATION IS INCREASED (see ADVERSE REACTIONS, Renal Toxicity).

- **ZOMETA TREATMENT IS NOT RECOMMENDED IN PATIENTS WITH BONE METASTASES WITH SEVERE RENAL IMPAIRMENT.** In the clinical studies, patients with serum creatinine >265 µmol/L or >3.0 mg/dL were excluded and there were only eight of 564 patients treated with Zometa 4 mg by 15-minute infusion with a baseline creatinine >2 mg/dL. Limited pharmacokinetic data exists in patients with creatinine clearance <30 mL/min (see CLINICAL PHARMACOLOGY).
- **PRE-EXISTING RENAL INSUFFICIENCY AND MULTIPLE CYCLES OF ZOMETA AND OTHER BISPHOSPHONATES ARE RISK FACTORS FOR SUBSEQUENT RENAL DETERIORATION WITH ZOMETA. FACTORS PREDISPOSING TO RENAL DETERIORATION, SUCH AS DEHYDRATION OR THE USE OF OTHER NEPHROTOXIC DRUGS, SHOULD BE IDENTIFIED AND MANAGED IF POSSIBLE.**
- **ZOMETA TREATMENT IN PATIENTS WITH HYPERCALCEMIA OF MALIGNANCY WITH SEVERE RENAL IMPAIRMENT SHOULD BE CONSIDERED ONLY AFTER EVALUATING THE RISKS AND BENEFITS OF TREATMENT.** In the clinical studies, patients with serum creatinine >400 µmol/L or >4.5 mg/dL were excluded.

Patients who receive Zometa should have serum creatinine assessed prior to each treatment. Patients treated with Zometa for multiple myeloma and bone metastases of solid tumors should have the dose withheld if renal function has deteriorated. (See DOSAGE AND ADMINISTRATION.) Patients with hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk.

PREGNANCY: ZOMETA SHOULD NOT BE USED DURING PREGNANCY. Zometa may cause fetal harm when administered to a pregnant woman. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure (an IV dose of 4 mg based on an AUC comparison) resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations. (See PRECAUTIONS, Pregnancy Category D.)

There are no studies in pregnant women using Zometa. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zometa® (zoledronic acid) Injection. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

Renal Insufficiency

Limited clinical data are available regarding use of Zometa in patients with renal impairment. Zometa is excreted intact primarily via the kidney, and the risk of adverse reactions, including renal adverse reactions, may be greater in patients with impaired renal function. Serum creatinine should be monitored in all patients treated with Zometa prior to each dose.

Studies of Zometa in the treatment of hypercalcemia of malignancy excluded patients with serum creatinine >400 µmol/L or >4.5 mg/dL. Bone metastases trials excluded patients with serum creatinine >265 µmol/L or >3.0 mg/dL and there were only eight of 564 patients treated with Zometa 4 mg by 15-minute infusion with a baseline serum creatinine >2 mg/dL. Limited pharmacokinetic data are available to guide dose selection or to provide guidance with respect to safely use Zometa in patients with severe renal impairment. For multiple myeloma and bone metastases of solid tumors, the use of Zometa in patients with severe renal impairment is not recommended. For hypercalcemia of malignancy, Zometa should be used in patients with severe renal impairment only if the expected clinical benefits outweigh the risk of renal failure after considering other available treatment options. (See WARNINGS.) Dose adjustments in patients are not necessary in treating patients for hypercalcemia presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine <400 µmol/L or <4.5 mg/dL).

Patients receiving Zometa for hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated and consideration should be given as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk.

Upon initiation of treatment in patients with multiple myeloma or metastatic bone disease and solid tumors, with mild-to-moderate renal impairment, lower doses of Zometa are not required. In patients who show evidence of renal deterioration during treatment, Zometa should be withheld and resumed when serum creatinine returns to within 10% of baseline. (See WARNINGS, DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

Only limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance with respect to dosage selection or how to safely use Zometa in these patients.

Patients with Asthma

While not observed in clinical trials with Zometa, administration of other bisphosphonates has been associated with bronchoconstriction in aspirin-sensitive asthmatic patients. Zometa should be used with caution in patients with aspirin-sensitive asthma.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. However, such reports are relatively infrequent. This category of drugs includes Zometa (zoledronic acid) Injection. The majority of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Laboratory Tests

Serum creatinine should be monitored prior to each dose of Zometa. Serum calcium, serum phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly. (See WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS.)

Drug Interactions

In vitro studies indicate that zoledronic acid is approximately 22% bound to plasma proteins. *In vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine unchanged. However, no *in vivo* drug interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides because both agents may have an additive effect to lower serum calcium level for prolonged periods. This was not been reported in Zometa clinical trials. Caution should also be exercised when Zometa is used in combination with loop diuretics due to an increased risk of hypocalcemia. Concomitant use of Zometa is used with other potentially nephrotoxic drugs.

In multiple myeloma patients, the risk of renal dysfunction may be increased when Zometa is used in combination with thalidomide.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥0.002 times a human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≤0.2 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas).

Mutagenesis: Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, a Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus test.

Impairment of Fertility: Female rats were given subcutaneous doses of zoledronic acid of 0.001, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on AUC comparison) included irregular estrous cycles, ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid- and high-dose group (with systemic exposure of 0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and high-dose group included an increase in the number of implantations and live fetuses.

Pregnancy Category D (See WARNINGS.)

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest

Zometa®
(zoledronic acid)

Zometa®
(zoledronic acid)

cid) Injection

e is greater than into maternal bone. Therefore, there is a theo-
letal and other abnormalities) if a woman becomes pregnant
osphonate therapy. The impact of variables such as time
nate therapy to conception, the particular bisphosphonate used,
travenous versus oral) on this risk has not been established.
ous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day
and continuing through gestation, the number of stillbirths was
as was decreased in the mid- and high-dose groups (≥0.2 times
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ere observed in all dose groups (with a systemic exposure of
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fects were observed in the mid- and high-dose groups (with sys-
mes, respectively, the human systemic exposure following an
l on an AUC comparison). These adverse effects included
ntation losses, decreases in viable fetuses, and fetal skeletal, vis-
s. Fetal skeletal effects observed in the high-dose group included
d bones, thickened, curved or shortened bones, wavy ribs, and
al effects observed in the high-dose group included reduced lens.
n or absence of liver lobes, reduction of lung lobes, vessel dila-
eletal variations were also observed in the low-dose group (with
e human systemic exposure following an intravenous dose of 4 mg,
igns of maternal toxicity were observed in the high-dose group
ghts and food consumption, indicating that maximal exposure
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utaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day
aman intravenous dose of 4 mg, based on a comparison of relative
fetal effects were observed. Maternal mortality and abortion
(at doses ≥0.05 times the human intravenous dose of 4 mg,
e body surface areas). Adverse maternal effects were associated
d by, drug-induced hypocalcemia.

is excreted in human milk. Because many drugs are excreted in
ta binds to bone long term, Zometa should not be administered to

Zometa in pediatric patients have not been established. Because
Zometa should only be used in children if the potential benefit out-

percalcemia of malignancy included 34 patients who were 65
ant differences in response rate or adverse reactions were seen
mets as compared to younger patients. Controlled clinical studies
ultiple myeloma and bone metastases of solid tumors in patients
acy and safety in older and younger patients. Because decreased
monly in the elderly, special care should be taken to monitor renal

(zoledronic acid) injection are usually mild and transient and simi-
isphosphonates. Intravenous administration has been most com-
ccasionally, patients experience a flu-like syndrome consisting of
and/or arthralgias, and myalgias. Gastrointestinal reactions such
een reported following intravenous infusion of Zometa. Local reac-
ts redness or swelling, were observed infrequently. In most cases,
d and the symptoms subside after 24-48 hours.
, and chest pain have been reported following treatment with

ses, cases of conjunctivitis and hypomagnesemia have been
th Zometa.
atory abnormalities for serum creatinine, serum calcium, serum
esium observed in two clinical trials of Zometa in patients with HCM

ory Abnormalities for Serum Creatinine, Serum Calcium, s, and Serum Magnesium in Two Clinical Trials in Patients

Grade 3			Grade 4			
Zometa® mg (%)	Pamidronate 90 mg n/N	(%)	Zometa® 4 mg n/N	(%)	Pamidronate 90 mg n/N	(%)
(2.3%)	3/100	(3.0%)	0/86	—	1/100	(1.0%)
(1.2%)	2/100	(2.0%)	0/86	—	0/100	—
(51.4%)	27/81	(33.3%)	1/70	(1.4%)	4/81	(4.9%)
—	0/84	—	0/71	—	1/84	(1.2%)

Normal); Grade 4 (>6x Upper Limit of Normal)
i (<6 mg/dL)
i (<1 mg/dL)
s 4 (<0.5 mEq/L)

Table 7 provides adverse events that were reported by 10% or more of the 189 patients treated with Zometa 4 mg or pamidronate 90 mg from the two controlled multicenter HCM trials. Adverse events are listed regardless of presumed causality to study drug.

Table 7: Percentage of Patients with Adverse Events ≥10% Reported in Hypercalcemia of Malignancy Clinical Trials by Body System

	Zometa® 4 mg n (%)	Pamidronate 90 mg n (%)
Patients Studied	86 (100)	103 (100)
Total No. of Patients Studied	81 (94.2)	95 (92.2)
Total No. of Patients with any AE		
Body as a Whole	38 (44.2)	34 (33.0)
Fever	14 (16.3)	21 (20.4)
Progression of Cancer		
Digestive	25 (29.1)	28 (27.2)
Nausea	23 (26.7)	13 (12.6)
Constipation	15 (17.4)	17 (16.5)
Diarrhea	14 (16.3)	13 (12.6)
Abdominal Pain	12 (14.0)	17 (16.5)
Vomiting	8 (9.3)	14 (13.6)
Anorexia		
Cardiovascular	9 (10.5)	2 (1.9)
Hypotension		
Hemic and Lymphatic System	19 (22.1)	18 (17.5)
Anemia		
Infections	10 (11.6)	4 (3.9)
Moniliasis		
Laboratory Abnormalities	11 (12.8)	2 (1.9)
Hypophosphatemia	10 (11.6)	16 (15.5)
Hypokalemia	9 (10.5)	5 (4.9)
Hypomagnesemia		
Musculoskeletal	10 (11.6)	10 (9.7)
Skeletal Pain		
Nervous	13 (15.1)	10 (9.7)
Insomnia	12 (14.0)	8 (7.8)
Anxiety	11 (12.8)	13 (12.6)
Confusion	11 (12.8)	8 (7.8)
Agitation		
Respiratory	19 (22.1)	20 (19.4)
Dyspnea	10 (11.6)	12 (11.7)
Coughing		
Urogenital	12 (14.0)	15 (14.6)
Urinary Tract Infection		

The following adverse events from the two controlled multicenter HCM trials (n=189) were reported by a greater percentage of patients treated with Zometa 4 mg than with pamidronate 90 mg and occurred with a frequency of greater than or equal to 5% but less than 10%. Adverse events are listed regardless of presumed causality to study drug.

Body as a Whole: asthenia, chest pain, leg edema, mucositis, and metastases
Digestive System: dysphagia
Hemic and Lymphatic System: granulocytopenia, thrombocytopenia, and pancytopenia
Infection: non-specific infection
Laboratory Abnormalities: hypocalcemia
Metabolic and Nutritional: dehydration
Musculoskeletal: arthralgias
Nervous System: headache, somnolence
Respiratory System: pleural effusion

NOTE: In the HCM clinical trials, pamidronate 90 mg was given as a 2-hour intravenous infusion. The relative safety of pamidronate 90 mg given as a 2-hour intravenous infusion compared to the same dose given as a 24-hour intravenous infusion has not been adequately studied in controlled clinical trials.

Multiple Myeloma and Bone Metastases of Solid Tumors
The safety analysis includes patients treated in the core and extension phases of the trials. The analysis includes the 2,042 patients treated with Zometa 4 mg, pamidronate 90 mg or placebo in the three controlled multicenter bone metastases trials, including 969 patients completing the efficacy phase of the trial, and 619 patients that continued in the safety extension phase. Only 347 patients completed the extension phases and were followed for two years (or 21 months for the other solid tumor patients). The median duration of exposure for safety analysis for Zometa 4 mg (core plus extension phases) was 12.8 months for breast cancer and multiple myeloma, 10.8 months for prostate cancer, and 4.0 months for other solid tumors.

Table 8 describes adverse events that were reported by ≥10% of patients. Adverse events are listed regardless of presumed causality to study drug.

Table 8: Percentage of Patients with Adverse Events ≥10% Reported in Three Bone Metastases Clinical Trials by Body System

	Zometa® 4 mg n (%)	Pamidronate 90 mg n (%)	Placebo n (%)
Patients Studied	1031 (100)	556 (100)	455 (100)
Total No. of Patients	1015 (98)	548 (99)	445 (98)
Total No. of Patients with any AE			
Blood and Lymphatic	344 (33)	175 (32)	128 (28)
Anemia	124 (12)	83 (15)	35 (8)
Neutropenia	102 (10)	53 (10)	20 (4)
Thrombocytopenia			
Gastrointestinal	476 (46)	266 (48)	171 (38)
Nausea	333 (32)	183 (33)	122 (27)
Vomiting	320 (31)	162 (29)	174 (38)
Constipation	249 (24)	162 (29)	83 (18)
Diarrhea	143 (14)	81 (15)	48 (11)
Abdominal Pain	105 (10)	74 (13)	31 (7)
Dyspepsia	86 (8)	65 (12)	14 (3)
Stomatitis	82 (8)	61 (11)	17 (4)
Sore Throat			
General Disorders and Administration Site	398 (39)	240 (43)	130 (29)
Fatigue	328 (32)	172 (31)	89 (20)
Pyrexia	252 (24)	108 (19)	114 (25)
Weakness	215 (21)	125 (23)	84 (19)
Edema Lower Limb	112 (11)	62 (11)	28 (6)
Rigors			
Infections	124 (12)	50 (9)	41 (9)
Urinary Tract Infection	101 (10)	82 (15)	30 (7)
Upper Respiratory Tract Infection			
Metabolism	231 (22)	81 (15)	105 (23)
Anorexia	164 (16)	50 (9)	61 (13)
Weight Decreased	145 (14)	60 (11)	59 (13)
Dehydration	130 (13)	48 (9)	45 (10)
Appetite Decreased			
Musculoskeletal	569 (55)	316 (57)	284 (62)
Bone Pain	239 (23)	143 (26)	74 (16)
Myalgia	216 (21)	131 (24)	73 (16)
Arthralgia	156 (15)	106 (19)	40 (9)
Back Pain	143 (14)	84 (15)	52 (11)
Pain in Limb			
Neoplasms	205 (20)	97 (17)	89 (20)
Malignant Neoplasm Aggravated			
Nervous	191 (19)	149 (27)	50 (11)
Headache	180 (18)	91 (16)	58 (13)
Dizziness (excluding vertigo)	166 (16)	111 (20)	73 (16)
Insomnia	149 (15)	85 (15)	35 (8)
Paresthesia	127 (12)	66 (12)	43 (10)
Psychiatric	146 (14)	95 (17)	49 (11)
Depression	112 (11)	73 (13)	37 (8)
Anxiety	74 (7)	39 (7)	47 (10)
Confusion			
Respiratory	282 (27)	155 (28)	107 (24)
Dyspnea	224 (22)	129 (23)	65 (14)
Cough			
Skin	125 (12)	80 (14)	36 (8)
Alopecia	114 (11)	74 (13)	38 (8)
Dermatitis			

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in three clinical trials of Zometa in patients with bone metastases are shown in Tables 9 and 10.

Table 9: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

	Grade 3					
Laboratory Parameter	Zometa® 4 mg n/N	(%)	Pamidronate 90 mg n/N	(%)	Placebo n/N	(%)
Serum Creatinine[1*]	7/529	(1.3%)	4/268	(1.5%)	4/241	(1.7%)
Hypocalcemia[2]	6/973	(0.6%)	4/536	(0.7%)	0/415	—
Hypophosphatemia[3]	115/973	(11.8%)	38/537	(7.1%)	14/415	(3.4%)
Hypermagnesemia[4]	19/971	(2.0%)	2/535	(0.4%)	8/415	(1.9%)
Hypomagnesemia[5]	1/971	(0.1%)	0/535	—	1/415	(0.2%)

[1] Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)
[*] Serum creatinine data for all patients randomized after the 15-minute infusion amendment
[2] Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3] Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4] Grade 3 (>3 mEq/L); Grade 4 (>8 mEq/L)
[5] Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Table 10: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

	Grade 4					
Laboratory Parameter	Zometa® 4 mg n/N	(%)	Pamidronate 90 mg n/N	(%)	Placebo n/N	(%)
Serum Creatinine[1*]	2/529	(0.4%)	1/268	(0.4%)	0/241	—
Hypocalcemia[2]	7/973	(0.7%)	3/536	(0.6%)	2/415	(0.5%)
Hypophosphatemia[3]	5/973	(0.5%)	0/537	—	1/416	(0.2%)
Hypermagnesemia[4]	0/971	—	0/535	—	2/415	(0.5%)
Hypomagnesemia[5]	2/971	(0.2%)	1/535	(0.2%)	0/416	—

[1] Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)
[*] Serum creatinine data for all patients randomized after the 15-minute infusion amendment
[2] Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3] Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4] Grade 3 (>3 mEq/L); Grade 4 (>8 mEq/L)
[5] Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Among the less frequently occurring adverse events (<15% of patients), rigors, hypokalemia, influenza-like illness, and hypocalcemia showed a trend for more events with bisphosphonate administration (Zometa 4 mg and pamidronate groups) compared to the placebo group.

Less common adverse events reported more often with Zometa 4 mg than pamidronate included decreased weight, which was reported in 16% of patients in the Zometa 4-mg group compared with 9% in the pamidronate group. Decreased appetite was reported in slightly more patients in the Zometa 4-mg group (13%) compared with the pamidronate (9%) and placebo (10%) groups, but the clinical significance of these small differences is not clear.

Renal Toxicity
In the bone metastases trials, renal deterioration was defined as an increase of 0.5 mg/dL for patients with normal baseline creatinine (<1.4 mg/dL) or an increase of 1.0 mg/dL for patients with an abnormal baseline creatinine (≥1.4 mg/dL). The following are data on the incidence of renal deterioration in patients receiving Zometa 4 mg over 15 minutes in these trials. (See Table 11.)

Table 11: Percentage of Patients with Renal Function Deterioration Who Were Randomized Following the 15-Minute Infusion Amendment

Patient Population/Baseline Creatinine

Multiple Myeloma and Breast Cancer	Zometa® 4 mg n/N	(%)	Pamidronate 90 mg n/N	(%)
Normal	27/246	(11%)	23/246	(9.3%)
Abnormal	2/26	(7.7%)	2/22	(9.1%)
Total	29/272	(10.7%)	25/268	(9.3%)

Solid Tumors	Zometa® 4 mg n/N	(%)	Placebo n/N	(%)
Normal	17/154	(11%)	10/143	(7%)
Abnormal	1/11	(9.1%)	1/20	(5%)
Total	18/165	(10.9%)	11/163	(6.7%)

Prostate Cancer	Zometa® 4 mg n/N	(%)	Placebo n/N	(%)
Normal	12/82	(14.6%)	8/68	(11.8%)
Abnormal	4/10	(40%)	2/10	(20%)
Total	16/92	(17.4%)	10/78	(12.8%)

The risk of deterioration in renal function appeared to be related to time on study, whether patients were receiving Zometa (4 mg over 15 minutes), placebo, or pamidronate.

Evaluation of serum creatinine is recommended prior to each cycle of therapy with Zometa. In patients receiving Zometa for multiple myeloma and bone metastases of solid tumors, who show evidence of deterioration in renal function, Zometa treatment should be withheld until serum creatinine returns to within 10% of baseline.

In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis have occurred in patients with normal and abnormal baseline renal function, including patients treated with 4 mg infused over a 15-minute period. There have been instances of this occurring after the initial Zometa dose.

Post-Marketing Experience
Cases of osteonecrosis (primarily involving the jaws) have been reported in patients treated with bisphosphonates. The majority of the reported cases are in cancer patients attendant to a dental procedure. Osteonecrosis of the jaws has multiple well-documented risk factors including a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids) and comorbid conditions (e.g., anemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged. (See PRECAUTIONS.)

The following adverse reactions have been reported in post-marketing use:
CNS: tissue disturbance, hypersthesia, tremor; ***Special Senses:*** blurred vision; ***Gastrointestinal:*** dry mouth; ***Skin:*** increased sweating; ***Musculoskeletal:*** muscle cramps; ***Cardiovascular:*** hypertension, bradycardia, hypotension (associated with syncope or circulatory collapse usually in patients with underlying risk factors); ***Renal:*** hematuria, proteinuria; ***Allergic Reaction:*** hypersensitivity reaction, angioneurotic edema; ***General Disorders and Administration Site*** weight increase; ***Laboratory Abnormalities:*** hyperkalemia, hypernatremia.

Cases of uveitis and episcleritis have also been reported during post-marketing use.

OVERDOSAGE
There is no experience of acute overdose with Zometa® (zoledronic acid) injection. Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

In an open-label study of zoledronic acid 4 mg in breast cancer patients, a female patient received a single 48-mg dose of zoledronic acid in error. Two days after the overdose the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal, and the patient was discharged seven days after the overdose.

A patient with non-Hodgkin's lymphoma received zoledronic acid 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paresthesia and abnormal liver function tests with increased GGT (nearly 100U/L, each value unknown). The outcome of this case is not known.

In controlled clinical trials, administration of Zometa 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15-minute intravenous infusion. In controlled clinical trials, Zometa 8 mg has been shown to be associated with an increased risk of renal toxicity compared to Zometa 4 mg, even when given as a 15-minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy. **Single doses of Zometa should not exceed 4 mg and the duration of the intravenous infusion should be no less than 15 minutes. (See WARNINGS.) In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zometa dose.**

DOSAGE AND ADMINISTRATION

Hypercalcemia of Malignancy
Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Zometa® (zoledronic acid) injection. Vigorous saline hydration alone may be sufficient to treat mild, asymptomatic hypercalcemia.

The maximum recommended dose of Zometa in hypercalcemia of malignancy (albumin-corrected serum calcium* ≥12 mg/dL [3.0 mmol/L]) is 4 mg. The 4-mg dose must be given as a single-dose intravenous infusion over no less than 15 minutes.

Patients should be adequately rehydrated prior to administration of Zometa. (See WARNINGS and PRECAUTIONS.)

Retreatment with Zometa 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zometa and possible deterioration in renal function must be assessed prior to retreatment with Zometa. (See WARNINGS and PRECAUTIONS.)

*Albumin-corrected serum calcium (Cca, mg/dL) = Ca + 0.8 (mid-range albumin-measured albumin in mg/dL).

Multiple Myeloma and Metastatic Bone Lesions From Solid Tumors
The recommended dose of Zometa in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance >60 mL/min is 4 mg infused over no less than 15 minutes every three to four weeks. The optimal duration of therapy is not known.

Upon treatment initiation, the recommended Zometa doses for patients with reduced renal function (mild and moderate renal impairment) are listed in the following table. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula. (See CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency.)

Baseline Creatinine Clearance (mL/min)	Zometa® Recommended Dose*
> 60	4.0 mg
50 - 60	3.5 mg
40 - 49	3.3 mg
30 - 39	3.0 mg

*Doses calculated assuming target AUC of 0.66(mg•hr/L) (CrCl=75 mL/min)

During treatment, serum creatinine should be measured before each Zometa dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dL.
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dL.

In the clinical studies, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zometa should be re-initiated at the same dose as that prior to treatment interruption.

Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

Preparation of Solution
4-mg Dose: Vials of Zometa concentrate for infusion contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection. The dose must be given as a single intravenous infusion over no less than 15 minutes.
Reduced Doses for Patients with Baseline CrCl ≤60 mL/min: Withdraw an appropriate volume of the 5 mL - Zometa concentrate as needed:
4.4 mL for 3.5 mg dose
4.1 mL for 3.3 mg dose
3.8 mL for 3.0 mg dose
The withdrawn concentrate must be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. The dose must be given as a single intravenous infusion over no less than 15 minutes.
If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2°C-8°C (36°F-46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.
Zometa must not be mixed with calcium-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs.

Method of Administration: **Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Zometa should not exceed 4 mg and the duration of infusion should be no less than 15 minutes. (See WARNINGS.) In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zometa dose.**
There must be strict adherence to the intravenous administration recommendations for Zometa in order to decrease the risk of deterioration in renal function.

Note: **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

HOW SUPPLIED

Each 5-mL vial contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP, water for injection and 24 mg of sodium citrate, USP.
Carton of 1 vial ..... NDC 0078-0387-25

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

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NOVARTIS

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